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(54) Title: HYDRAULIC SURGICAL CEMENT

(57) Abstract

The cement for surgical purposes comprises three components. The first component comprises beta tertiary calciumphosphate β–$Ca_3(PO_4)_2$ (β–TCP) particles; and monocalcium phosphate $Ca(H_2PO_4)_2$ (MCPA) or monocalcium phosphate monohydrate $Ca(H_2PO_4).H_2O$ (MCPM) particles or phosphoric acid. The second component comprises water. The third component comprises particles having an average diameter which is larger than the average diameter of said beta tertiary calciumphosphate β–$Ca_3(PO_4)_2$ (β–TCP) particles of said first component. Upon mixing of said three components a hardened mass comprising brushite $CaHPO_4$. $2H_2O$ (DCPD) is formed. The β–TCP particles have a specific surface area of less than 10,000 m^2/g and a Ca/P atomic ratio different from 1,50. The component constitutes 1 to 99 volume–percent of said hardened mass. The cements according to the invention may be used in dental and maxillofacial surgery (alveolar ridge reconstruction, dental socket filling), for orthopaedic applications (bone fracture repair, bone augmentation) and for local drug delivery (antibiotics, anti–inflammatory and anti–cancer drugs).

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Hydraulic Surgical Cement

This invention concerns a cement for surgical purposes in accordance with the pre-characterising portion of Claim 1, a method for producing brushite as temporary bone replacement material according to the pre-characterising portion of Claim 34 and the temporary bone replacement material obtained by said method according to Claim 35.

A number of such hydraulic cements based on calcium phosphates for use in surgery are known in the prior art; they are prepared from two components (powder/liquid) by mixing them intra-operatively and applying them in pasteous consistency to the appropriate site where they harden in situ. The disadvantages of the prior art hydraulic cements based calcium phosphates are:

impracticable short setting times which do not allow their use for elaborate surgical procedures;

poor injectability, i.e. the fresh cement paste tends to clog the injection needle, and/or disintegrates in contact with physiological liquids, which prevents its implantation by minimal invasive surgery procedures;

low compacity, i.e. current hydraulic cements need larger amounts of mixing water in order to have them injectable or to confer them a convenient setting time, which results in very low ultimate mechanical strength after hardening.

In the US-A-4 880 610 CONSTANTZ a method is disclosed for making an in situ calcium phosphate mineral composition by combining water-free phosphoric acid crystals with a calcium source which leads to a hydroxyapatite. It is clear that the use of 100% phosphoric acid in the operating room and the application of a paste containing 100% phosphoric acid in the human body must be considered a not ideal procedure which requires improvement. Furthermore the hydroxyapatite material produced by this known method will have a long resorption period which is not commensurate to the rate of the bone remodelling. The disadvantage of prolonged resorption is that the bone treated by cement will remain for a prolonged time in abnormal biomechanical situation, which may develop secondary post-operational problems. Furthermore the unresorbed cement may still break down in pieces or fragments after prolonged mechanical loading, which increases the probability of post-operational complications, e.g. aseptic inflammatory reactions. The resorption rate of the ideal cement should match as closely possible the spontaneous rate of new bone formation, which is around 20 micrometers per day.

From GB-2 260 977 MITSUBISHI a calcium phosphate composition is known using alpha-TCP particles. Alpha-TCP particles are much more reactive than beta-TCP particles and therefore lead to a

setting time - when admixed to monocalcium phosphate monohydrate and water - that is much too fast (a few seconds), and hence difficult to control.

From an article of MIRCHI A A ET AL. appeared in Biomaterial 1989, Vol. 10, No. 9, 1 November 1989, pages 634 - 638, a calcium phosphate cement is known with commercially available MCPM and ß-TCP particles the Ca/P ratio of which is 1,50.
The disadvantages of ß-TCP particles with a Ca/P ratio of 1,50 is their relatively high reactivity which makes them inappropriate for a surgical cement.

The invention as claimed aims at solving the above described problems. The present invention provides a cement for surgical purposes as defined in Claim 1, a method for producing a temporary bone replacement material as defined in Claim 34 and a temporary bone replacement material as defined in claim 35.

The various features of novelty which characterize the invention are pointed out with particularity in the claims annexed to and forming part of this disclosure. For the better understanding of the invention, its operating advantages and specific objects attained by its use, reference should be done to the accompanying examples in which preferred embodiments of the invention are illustrated in detail.

The first component of the cement according to the invention comprises besides beta tertiary calciumphosphate ß-$Ca_3(PO_4)_2$ (ß-TCP) particles one of the following substances:

a) monocalcium phosphate $Ca(H_2PO_4)_2$ (MCPA) particles; or

b) monocalcium phosphate monohydrate $Ca(H_2PO_4)_2 \cdot H_2O$ (MCPM) particles;

c) or phosphoric acid.

Alternative a) and b) are the preferred ones; the phosphoric acid may be used either in solid or in liquid form.

The Ca/P atomic ratio of the ß-TCP particles of the first component is preferably comprised between 1,35 to 1,499. Purposefully it is comprised between 1,45 to 1,47 and typically between 1,455 to 1,465. The advantage of the Ca/P atomic ratio used in the invention is the lower reactivity of the ß-TCP particles. A lower Ca/P atomic ratio - below 1,5 - can be achieved in avarious ways. One possiblity is the calcination and sintering of DCP [$CaHPO_4$]/hydroxyapatite [$Ca_5(PO_4)_3OH$]) mixtures. The Ca/P ratio is then controlled by teh proportion of the two components. To obtain a Ca/P ratio of exactly 1,50 one should mix 10 g of DCP with 36,91 g HA. To obtain a Ca/P ratio of 1,35 one has to mix 10 g DCP with 13,6 g of HA. Alternatively DCP could be replaced by DCPD ($CaHPO_4 \cdot H_2O$), MCPM [$Ca(H_2PO_4)_2 \cdot H_2O$], CaPP ($Ca_2P_2O_7$) or OCP [$Ca_8H_2PO_4)_6 \cdot 5H_2O$]. The beta-TCP particles with a Ca/P ration inferior to 1,50 can also be obtained by adding small amounts of DCP, DCPD, MCPM or OCP to a pure beta-TCP powder, and then mix and sinter the mixture to homogenize it.

Onother way is to add minor amounts of $Na_4P_2O_7 \cdot 10\ H_2O$ (NaPPH) to the ß-TCP particles which retard their dissolution in a synergetic way. Consequently the setting time of the hydraulic cement is significantly increased. The presence of minor amounts of CaPPH increases also the sintering ability of the ß-TCP particles, hence enabling the production of dense ß-TCP particles. Non-dense ß-TCP particles absorb the mixing liquid during setting. As a following, more mixing liquid must be used to knead the cement, provoking a decrease of the mechanical properties of the cement after hardening.
If the amount of CaPPH is too large (Ca/P ratio below 1,35) the mechanical properties of the cement decrease drastically.

The mean specific surface area of the ß-TCP particles must be less than 10 m^2/g otherwise the cement has poor mechanical properties - due to a large porosity resulting from the large volume of mixing liquid - and a setting time which is too short for practical purposes.

Setting time of the cement according to the invention as measured at 25 C° should be at least 2 minutes, typically at least 3 minutes and preferably at least 5 minutes.

According to a preferred embodiment of the invention the first component is divided into two subcomponents A and B, subcomponent A comprising the MCPA and/or MCPM particles and subcomponent B comprising the ß-TCP particles and the setting rate controller.

The second component comprises water and may further comprise orthophosphoric acid (OPA) and/or sulphuric acid (SA), which again take the function of a setting rate controller and also lead to an improved microstructure of the final brushite (DCPD) crystals.

After mixing the three components a hardened mass is formed comprising brushite $CaHPO_4 \cdot 2\ H_2O$ (DCPD), which based on its solubility is used to accelerate the resorption rate compared to HA.

The total weight W_{TCP} of the ß-TCP particles of the first and third components should preferably be larger than the stoichiometric weight

$W_T = W_{MCPA}/0,7546 + W_{MCPM}/0,8127 + W_{OPA}/0,3159 + W_{SA}/0.3162$

where W_{MCPA}, W_{MCPM}, W_{OPA} and W_{SA} are, respectively, the weights of MCPA, MCPM, OPA and SA used.

Further the weight W_{TCP} should be in the range of $1,2\ W_T \leq W_{TCP} \leq 2,0\ W_T$.

The first component may further comprise a setting rate controller chosen from the group of sodium pyrophosphate, potassium pyrophosphate, sodium acetate, potassium acetate, sodium citrate, potassium citrate, sodium phosphocitrate, potassium phosphocitrate, sodium sulphate or potassium sulphate, calcium sulphate hemihydrate $CaSO_4 \cdot 0,5\ H_2O$ (CSH), sodium pyrophosphate $Na_4P_2O_7 \cdot 10\ H_2O$ (NaPPH), sodium dihydrogen pyrophosphate $Na_2H_2P_2O_7$ (NaHPP), calcium pyrophosphate $Ca_4P_2O_7$ (CaPP), magnesium sulphate and sodium or potassium biphosphonate.

In a further preferred embodiment of the invention a third component consisting of particles having an average diameter which is larger than the average diameter of said beta tertiary calciumphosphate ß-$Ca_3(PO_4)_2$ (ß-TCP) particles of said first component is added. This leads to conglomerate structure of the finally set cement, whereby the third component particles are embedded in the brushite matrix formed by the setting process. The average particle diameter of said third component should be at least two times larger, preferably at least 10 times larger compared to the average diameter of the beta tertiary calciumphosphate ß-$Ca_3(PO_4)_2$ (ß-TCP) particles of the first component. Preferably the average particle diameter of said third component should be in the range of 50 to 2000 µm. The particles of the third component may consist of hydroxyapatite particles or of polymeric particles, e.g. lactides, polysaccharides, collagenes or proteins.

In a further preferred embodiment of the invention two different types of ß-TCP particles are used, the first type being particles having a median particle size of 5 µm with less than 10 volume % of the particles being smaller than 1 µm; and the second type being particles having an average diameter in the range of 150 to 400 µm, preferably in the range of 250 to 350 µm.

The average particle diameter of said third component should be in the range of 50 to 2000 µm, preferably between 250 and 750 µm.

The volume V_L of the second component should preferably be equal or superior than the volume V_T = (W_{MCPA} x 0,615 + W_{MCPM} x 0,5 + W_{OPA} x 1,102 + W_{SA} x 1,101) ml/g of the first component. The volume V_L is typically in the range of 0,5 $V_T \leq V_L \leq$ 10,0 V_T, preferably in the range of 1,2 $V_T \leq V_L \leq$ 2,0 V_T.

One of the two components may further comprise a biodegradable polymer for controlling the consistency of the cement paste resulting from mixing of the two components, and its cohesion in physiological liquids.

The biodegradable polymer may be selected from the group of polysaccharide derivatives, preferably hyaluronic acid, dextran, hydroxypropyl-methyl cellulose; chitin derivatives, preferably chitosan; xanthan gum; agarose; polyethyleneglycols (PEG), polyhydroxyethylenemethacrylats (HEMA), synthetic and natural proteins or collagens.

The first component may further comprise pharmaceutically or physiologically active substances, preferably selected from the group of antibiotics, anti-inflammatory, anti-cancer drugs and bone growth factors. The antibiotics is preferably a gentamycin or a gentamycin salt, typically gentamycin sulphate. Other gentamycin salts can be used provided their solubility is in the range of 100 to 2500 mg/l.

The antibiotics is selected from the group of aminoglycosides, vancomycins, gentamycins or salts thereof, preferably gentamycin sulphate or gentamycin crobefat.

The cements according to the invention may be used as bone substitute in dental and maxillofacial surgery (alveolar ridge reconstruction, dental socket filling), for orthopaedic applications (bone fracture repair, bone augmentation) and for local drug delivery (antibiotics, anti-inflammatory and anti-cancer drugs).

In a preferred embodiment the particles of the third component are made from another material than beta tertiary calciumphosphate ß-$Ca_3(PO_4)_2$ (ß-TCP).

The particles of said third component are preferably made from a material selected from the group of:

hydroxylapatite; biphasic calcium phosphonate (BCP) (HA/ß-TCP) mixtures; bioglasses; or polymeric materials.

The advantage is the differential degradation of such a cement. The matrix of the cement is degraded faster than the residual granulates. This is particularly useful for the application in the osteoporose field or for the ridge reconstruction of the jaw, where a slower degrading granulate, e.g.made from hydroxyapatite or BCP is desired.

Five specific examples are reported below for producing the temporary bone replacement materials according to the invention.

Example 1

The first component (containing the powdered particles) consists of two separate subcomponents A and B.

Subcomponent A consist of:

0,80 g of monocalcium phosphate monohydrate $Ca(H_2PO_4)_2 \cdot H_2O$ MCPM particles.

Subcomponent B is a mixture of:

1,20 g of beta tertiary calciumphosphate ß-$Ca_3(PO_4)_2$ (ß-TCP) particles having a Ca/P atomic ratio in the range of 1,44 to 1,47. The median particle size of the ß-TCP particles is 5 μm and its specific surface area is less than 2 m^2/g; and

0,012 g sodium pyrophosphate $Na_2H_2P_2O_7$.

The second component (containing the liquid) consists of 0,80 to 0,90 ml of a 0,10 M aqueous sulphuric acid solution.

The third component - which may be admixed to the first component as Subcomponent C - contains 0,5 g (ß-TCP) particles with a diameter comprised in the range of 0,5 to 0,71 mm and a Ca/P atomic ratio in the range of 1,46.

The powdered subcomponents are sterilized by gamma-irradiation. The liquid component is prepared in sterile conditions with sterile materials.

The hydraulic cement paste is prepared by using a pestle. Subcomponent A is carefully mixed with the liquid component in a mortar for approximately 1 minute. Thereafter subcomponent B is added and kneaded carefully with a spatula for about a minute, until a uniform paste is obtained.
The paste can be used for about 10 minutes, depending on ambient temperature; the higher the temperature, the shorter the setting time. Using refrigerated material and preparation instruments helps in prolonging the available working time.

Example 2

The first component (containing the powdered particles) consists of 1,3 g of ß-TCP particles with an average diameter of 6 μm and a Ca/P molar ratio of 1,41 and 0,7 g of MCPM. The third component is added to the first component and comprises 0,3 g of ß-TCP particles with an average diameter comprised in the range of 0,35 to 0,50 mm and a Ca/P molar ratio of 1,42.
The second (liquid) component is a solution of 100 mg gentamycin sulphate in 1,6 ml of water.

The powder/liquid components were mixed together for 30 seconds and the resulting cement paste was filled into a syringe for application to a bone defect.

Example 3

The first component (containing the powdered particles) consists of 1,3 g of ß-TCP particles with an average diameter of 6 μm and a Ca/P molar ratio of 1,41 and 0,7 g of MCPM. The third component is added to the first component and comprises 0,8 g of hydroxyapatite (HA) particles with an average diameter comprised in the range of 0,35 to 0,50 mm. The second (liquid) component is a solution of 100 mg gentamycin sulphate in 1,6 ml of a 0,16 M aqueous sulphuric acid solution.

The powder/liquid components were mixed together for 30 seconds and the resulting cement paste was filled into a syringe for application to a bone defect.

Example 4

1,5 g of ß-TCP particles with an average diameter of 2 μm and a Ca/P molar ratio of 1,46, 0,3 g ß-TCP particles with an average diameter comprised in the range of 0,35 to 0,50 mm and a Ca/P molar ratio of 1,42 and 1,5 ml of a solution of H_3PO_4 3M, H_2SO_4 0,1 M and $Na_2H_2P_2O_7$ 0,1 M were mixed together for 30 seconds, placed into a syringe and injected into a bony cavity.

Example 5

1,5 g of ß-TCP particles with an average diameter of 2 μm and a Ca/P molar ratio of 1,46, 0,3 g hydroxyapatite (HA) particles with an average diameter comprised in the range of 0,35 to 0,50 mm and 1,5 ml of a solution of H_3PO_4 3M, H_2SO_4 0,1 M and

$Na_2H_2P_2O_7$ 0,1 M were mixed together for 30 seconds, placed into a syringe and injected into a bony cavity.

Claims

1. Cement for surgical purposes comprising

a first component comprising

beta tertiary calciumphosphate ß-$Ca_3(PO_4)_2$ (ß-TCP) particles; and

monocalcium phosphate $Ca(H_2PO_4)_2$ (MCPA) or monocalcium phosphate monohydrate $Ca(H_2PO_4)_2 \cdot H_2O$ (MCPM) particles or phosphoric acid;

a second component comprising
water; and

a third component comprising particles having an average diameter which is larger than the average diameter of said beta tertiary calciumphosphate ß-$Ca_3(PO_4)_2$ (ß-TCP) particles of said first component.

whereby upon mixing of said three components a hardened mass comprising brushite $CaHPO_4 \cdot 2H_2O$ (DCPD) is formed,

characterized in that

a) the ß-TCP particles have a mean specific surface area of less than 10,000 m^2/g;

b) the third component is a calcium phosphate with a Ca/P ratio different from 1,5; and

c) the third component constitutes 1 to 99 volume-percent of said hardened mass.

2. Cement according to claim 1, characterized in that said first component comprises beta tertiary calciumphosphate ß-$Ca_3(PO_4)_2$ (ß-TCP) particles and monocalcium phosphate $Ca(H_2PO_4)_2$ (MCPA) or monocalcium phosphate monohydrate $Ca(H_2PO_4)_2 \cdot H_2O$ (MCPM) particles.

3. Cement according to claim 1 or 2, characterized in that the setting time of said cement as measured at 25 C° is at least 2 minutes, preferably at least 3 minutes.

4. Cement according to claim 3, characterized in that the setting time of said cement as measured at 25 C° is at least 5 minutes.

5. Cement according to one of the claims 1 to 4, characterized in that the ß-TCP particles have a mean specific surface area of 0,0137 - 2,000 m^2/g.

6. Cement according to claim 5, characterized in that the ß-TCP particles have a mean specific surface area of 0,8 - 1,5 m^2/g.

7. Cement according to one of the claims 1 to 3, characterized in that the first component further comprises a setting rate controller.

8. Cement according to claim 7, characterized in that the first component is divided into three subcomponents X, Y and Z, subcomponent X comprising the MCPA and/or MCPM particles, subcomponent Y comprising the ß-TCP particles and the setting rate controller and subcomponent Z comprising the third component.

9. Cement according to claim 7 or 8, characterized in that the setting rate controller is chosen from the group of sodium pyrophosphate, potassium pyrophosphate, sodium acetate, potassium acetate, sodium citrate, potassium citrate, sodium phosphocitrate, potassium phosphocitrate, sodium sulphate or potassium sulphate, calcium sulphate hemihydrate $CaSO_4 \cdot 0,5\ H_2O$ (CSH), sodium pyrophosphate $Na_4P_2O_7 \cdot 10\ H_2O$ (NaPPH), sodium dihydrogen pyrophosphate $Na_2H_2P_2O_7$ (NaHPP), calcium pyrophosphate $Ca_4P_2O_7$ (CaPP), magnesium sulphate and sodium or potassium biphosphonate.

10. Cement according to one of the claims 1 to 9, characterized in that said second component further comprises orthophosphoric acid (OPA) and/or sulphuric acid (SA).

11. Cement according to one of the claims 1 to 10, characterized in that the total weight W_{TCP} of the ß-TCP particles of the first and third component is larger than the weight
$W_T = W_{MCPA}/0,7546 + W_{MCPM}/0,8127 + W_{OPA}/0,3159 + W_{SA}/0,3162$
where W_{MCPA}, W_{MCPM}, W_{OPA} and W_{SA} are, respectively, the weights of MCPA, MCPM, OPA and SA used.

12. Cement according to claim 11, characterized in that the weight W_{TCP} is in the range of $1,2\ W_T \leq W_{TCP} \leq 10,0\ W_T$.

13. Cement according to claim 12, characterized in that the weight W_{TCP} is in the range of $2\ W_T \leq W_{TCP} \leq 5\ W_T$.

14. Cement according to one of the claims 1 to 13, characterized in that the average particle diameter of said third component is at least two times, preferably at least 10 times larger than the average diameter of said beta tertiary calciumphosphate ß-$Ca_3(PO_4)_2$ (ß-TCP) particles of said first component.

15. Cement according to one of the claims 1 to 14, characterized in that the average particle diameter of said third component is in the range of 50 to 2000 μm, preferably between 250 and 750 μm.

16. Cement according to one of the claims 1 to 15, characterized in that said third component comprises hydroxyapatite particles.

17. Cement according to one of the claims 1 to 15, characterized in that said third component comprises polymeric particles.

18. Cement according to one of the claims 1 to 17, characterized in that two different types of ß-TCP particles are used,

the first type being particles having a median particle size of 5 µm with less than 10 volume % of the particles being smaller than 1 µm; and

the second type being particles having an average diameter in the range of 150 to 500 µm, preferably in the range of 250 to 400 µm.

19. Cement according to one of the claims 1 to 18, characterized in that the Ca/P atomic ratio of the ß-TCP particles of said first component is comprised between 1,350 to 1,499, preferably between 1,45 to 1,47.

20. Cement according to claim 19, characterized in that said Ca/P atomic ratio is comprised between 1,455 to 1,465.

21. Cement according to one of the claims 1 to 20, characterized in that one of the two components further comprises a biodegradable polymer.

22. Cement according to claim 21, characterized in that the biodegradable polymer is selected from the group of

polysaccharide derivatives, preferably hyaluronic acid, dextran, hydroxypropyl-methyl cellulose;

chitin derivatives, preferably chitosan;

xanthan gum;

agarose;

polyethyleneglycols (PEG), polyhydroxyethylenemethacrylats (HEMA);

synthetic and natural proteins; or

collagens.

23. Cement according to one of the claims 1 to 22, characterized in that the volume V_L of the second component is equal or larger than the volume

$V_T = (W_{MCPA} \times 0,615 + W_{MCPM} \times 0,5 + W_{OPA} \times 1,102 + W_{SA} \times 1,101)$ ml/g

24. Cement according to one of the claims 1 to 23, characterized in that the relation of volume V_L of the second component and of V_T of the first component is in the range of $0,5\ V_T \leq V_L \leq 10,0\ V_T$, preferably in the range of $1,2\ V_T \leq V_L \leq 2,0\ V_T$.

25. Cement according to one of the claims 1 to 24, characterized in that said first component further comprises pharmaceutically or physiologically active substances, preferably selected from the group of antibiotics, anti-inflammatory, anti-cancer drugs and bone growth factors.

26. Cement according to claim 25, characterized in that said antibiotics is selected from the group of:
aminoglycosides, vancomycins, gentamycins or salts thereof, preferably gentamycin sulphate or gentamycin crobefat.

27. Cement according to claim 26, characterized in that said antibiotics is a mixture of aminoglycosides, preferably a mixture of vancomycin with gentamycin.

28. Cement according to one of the claims 1 to 27, characterized in that the first component comprises at least 50 weight percent of beta tertiary calciumphosphate ß-$Ca_3(PO_4)_2$ (ß-TCP).

29. Cement according to one of the claims 1 to 28, characterized in that the particles of said third component are made from another material than beta tertiary calciumphosphate ß-$Ca_3(PO_4)_2$ (ß-TCP).

30. Cement according to claim 29, characterized in that the particles of said third component are made from a material selected from the group of:
hydroxylapatite;
biphasic calcium phosphonate (HA/ß-TCP) mixtures;
bioglasses;
or polymeric materials.

31. Cement according to one of the claims 1 to 30, characterized in that the third component constitutes 1 to 99 volume-percent of said hardened mass.

32. Cement according to one of the claims 1 to 31, characterized in that the third component is a calcium phosphate with a Ca/P ratio lower than 1,5, preferably in the range of 1,35 to 1,49.

33. Cement according to one of the claims 1 to 31, characterized in that the third component is a calcium phosphate with a Ca/P ratio higher than 1,5, preferebaly hydroxyapatite.

34. Method for producing a matrix of brushite $CaHPO_4 \cdot 2H_2O$ (DCPD) as temporary bone replacement material characterized in that said two components according to one of the claims 1 to 33 are mixed together and allowed to harden.

35. Temporary bone replacement material obtained by the method according to claim 34, characterized in that it comprises brushite $CaHPO_4 \cdot 2H_2O$ (DCPD).

36. Temporary bone replacement material according to claim 34, characterized in that it comprises beta tertiary calciumphosphate ß-$Ca_3(PO_4)_2$ (ß-TCP) particles embedded in said brushite matrix.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/06330

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K6/033 A61L25/00 A61L27/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MIRTCHI A A ET AL: "CALCIUM PHOSPHATE CEMENTS: ACTION OF SETTING REGULATORS ON THE PROPERTIES OF THE -TRICALCIUM PHOSPHATE- MONOCALCIUM PHOSPHATE CEMENTS" BIOMATERIALS, vol. 10, no. 9, 1 November 1989, pages 634-638, XP000081742 cited in the application	1-9, 11-16, 19,23, 24,28-36
Y	see abstract see page 634, right-hand column, paragraph 2 - page 635, left-hand column, paragraph 3 see page 636, right-hand column, paragraph 1 - page 637	21,22, 25-27

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
11 February 1999	19/02/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Heck, G

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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